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RELATIONSHIP BETWEEN UNSUPPLEMENTED VITAMIN A SERUM CONCENTRATIONS AND MEASLES VACCINE RESPONSE IN JAMAICAN CHILDREN

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THE PEDIATRIC INFECTIOUS DISEASE JOURNAL 1998;17:526-528

Key words: Vitamin A; measles; vaccine.

Vitamin A supplementation has been shown to reduce childhood morbidity and mortality rates.[1] Numerous experts and the World Health Organization (WHO) have recommended the initiation of vitamin A supplementation programs in many parts of the developing world.[1, 2] One of the few health care contacts at which vitamin A supplementation can be provided for many children occurs when routine childhood vaccinations are administered. Thus in 1986 the Global Advisory Group of the Expanded Programme on Immunization recommended that vitamin A supplementation be provided in conjunction with the administration of measles and other routine childhood vaccines.[2]

Recently, however, investigators have published findings suggesting that in some situations, the response to measles vaccination is altered by vitamin A supplementation.[3-5] One clinical trial from Indonesia found a lower rate of seroconversion after measles vaccination in 6-month-old vaccinees supplemented with vitamin A than in unsupplemented children.[4] A subsequent investigation of vitamin A supplementation in the same population did not find any effect in children who were vaccinated at 9 months.[5] However, a clinical trial from Guinea-Bissau suggested an improved vaccine response in vitamin A-supplemented compared with unsupplemented children vaccinated at 9 months, primarily for boys.[3] To date there has not been a study of the association between measured vitamin A serum concentrations and response to measles vaccination. The purpose of this study was to determine whether vitamin A serum concentrations bore a relationship to measles vaccine responsiveness.

Methods. Children for this nonconcurrent cohort study were recruited from a larger prospective study of Jamaican mothers and their infants that was originally developed to study risk factors for the transmission of human T cell leukemia/lymphoma virus type I (HTLV-I).[6] In this study consenting

pregnant mothers from two public antenatal clinics were tested for HTLV-I antibody and those found to be HTLV-I-seropositive were recruited, as were randomly chosen HTLV-I-seronegative mothers. The study protocol was approved by the Human Subjects Committees at the University of the West Indies, the National Cancer Institute and Johns Hopkins University and followed the human research guidelines for clinical research at each of these institutions. All children who were enrolled in the original study were included in the vitamin A study if they had the appropriate samples available for study.

The infants enrolled were evaluated from birth and at regularly scheduled well baby visits; every 6 weeks until 6 months of age, then every 3 months until 24 months. Each visit included a physical assessment and health status interview. Blood samples were collected at each visit, and vaccinations were administered according to WHO guidelines (measles vaccination with standard titer measles vaccine was offered at 9 months).

The analysis of measles vaccine response and vitamin A serum concentration was completed using the blood sample collected at the following times: for vitamin A analysis, the blood sample collected closest to the time of vaccination was used, and for the measles vaccine response the blood sample collected at the first clinic visit to follow measles vaccination was used. Some children did not have a blood sample available for vitamin A testing from the time of vaccination and so the next available sample (within 3 months) was used. The initial analysis of vaccine response included all children with a vitamin A sample collected within 3 months from the time of measles vaccination. To mitigate any potential impact from fluctuations in vitamin A serum concentrations between the time of measles vaccination and vitamin A measurement, a second analysis included only those children with a vitamin A sample collected close to the time that a response to the vaccine was occurring (set within 14 days). Children with a history of measles disease were excluded from this analysis, as was one child from any twin or sibling pair (thus antibody response measures could be assumed to be independent of each other).

Measles antibody testing was done with a commercial enzyme immunoassay specific for measles IgG (MEASELISA, BioWhittaker, Walkersville, MD). An antibody measure (MEASELISA value) of ≤0.13 was considered to be negative. High performance liquid chromatography extracted vitamin A from sera with the use of an equal volume of ethanol followed by a double extraction using hexane. The hexane extracts were evaporated under nitrogen and redissolved in ethanol aided by ultrasonic agitation. Samples were separated on a YMC ODS-AL® column with 85% acetonitrile/14% dioxane/1% methanol containing 0.01% triethylamine pumped at 2.0 ml/min (N. Craft, Craft Technologies, Inc., Wilson, NC).

Traditionally vitamin A status has been defined as: deficient, <0.35 μmol/l; low, 0.35 to 0.69 μmol/l; and normal, ≥0.70 μmol/l.[1] Because the number of vitamin A-deficient children was small in this study and because recent surveys[7, 8] have suggested that vitamin A serum concentrations ≥0.70 and ≤ 1.05 μmol/l may be inadequate, vitamin A serum concentrations for this analysis were divided into three groups: low, <0.70 μmol/l; borderline, ≥0.70 μmol/l and ≤1.05 μmol/l; and normal, >1.05 μmol/l. These three groups were used for the analysis of measles vaccine response with a continuous variable (antibody concentration). However, because there were small numbers of children in the lowest group, a precise analysis of the categoric variable, seroconversion, was difficult. Therefore the three vitamin A groups were reduced to two groups: low (≤1.05 μmol/l); and normal.

Relative risks and Fisher's exact test calculations were used for studying relationships between categoric variables. Square root transformations of antibody values were obtained to normalize

distributions, and statistical comparisons of antibody concentrations were completed by *t* test analysis of variance and linear regression. Spearman rank correlation analysis was used to obtain statistically robust measures of associations between vitamin A and measles antibody concentrations. When used, all confidence intervals were calculated at the 95% level.

Results. Of 239 children with samples available for study, 9 were excluded because they had a history of measles disease, 7 were excluded because they were part of a twin/sibling pair and 15 children were excluded because they had a vitamin A serum concentration obtained >3 months from the time of vaccination. Of the 208 children included in the initial analysis 128 (62%) were born to HTLV-I-infected mothers, 21 (10%) were HTLV-I-seropositive themselves, 114 (55%) were female and 118 (57%) were from low income families (≤$40 US, weekly). The median age of measles vaccination was 9.6 months (range, 8.0 to 19.4), the median age at the follow-up visit was 11.9 months (range, 9.4 to 29.4), the median duration between measles vaccination and follow-up visit was 2.5 months (range, 27 days to 11.9 months).

The majority, 127 (61%), of the 208 children tested had vitamin A serum concentrations below 1.05 μmol/l, with 43 of the 208 children (21%) having vitamin A serum concentrations < 0.70 μmol/l (Table 1). Of the 43 with vitamin A serum concentrations <0.70 μmol/l, 9 children had serum concentrations <0.35 μmol/l and 34 had serum concentrations between 0.35 and 0.69 μmol/l. The mean vitamin A serum concentration was 0.95 μmol/l (range, 0.18 to 1.86 μmol/l). The mean vitamin A serum concentrations were similar for male and female children (0.92 and 0.97 μmol/l, respectively) ($P = 0.33$). Four (4%) girls and 5 (5%) boys had concentrations < 0.35 μmol/l and 17 (18%) boys and 17 (15%) girls had concentrations between 0.35 and 0.69 μmol/l.

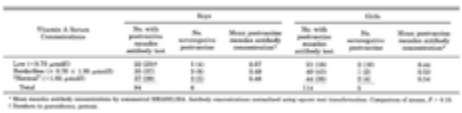

TABLE 1. Seronegative rates and measles antibody concentrations for Jamaican boys and girls vaccinated at 9 months by vitamin A serum concentration

Eleven (5%) of the 208 children were seronegative after vaccination. There was no association between an altered measles vaccine response and HTLV-I seropositivity [the relative risk for being measles antibody-seronegative after measles vaccination for children with mothers who were seropositive for HTLV-I compared with seronegative mothers was 1.1 (95% confidence interval (CI), 0.3 to 3.7); the relative risk for being measles antibody-seronegative after measles vaccination for children who were seropositive for HTLV-I compared with seronegative children was 0.4 (95% CI, 0.02 to 6.1)]. The mean postvaccination MEASELISA value was 0.51 for both the normal and low vitamin A groups (ranges, 0.03 to 1.38 and 0.01 to 1.42, respectively). The relative risk for being measles antibody-seronegative after measles vaccination for children with a vitamin A serum concentration ≤1.05 μmol/l compared with children with a vitamin A serum concentration >1.05 μmol/l was 1.1 (95% CI, 0.3 to 3.7). Vitamin A serum concentration and postvaccination MEASELISA values were not correlated ($r = 0.02$, $P = 0.73$). Because Benn et al.[3] found an interaction between gender and vitamin A supplementation, an interaction term was put into a model and no significant effect on measles vaccine response was detected. In this model children who had low vitamin A serum concentrations, borderline serum concentrations or "normal" serum concentrations had similar measles postvaccination antibody concentrations ($P = 0.98$). Limiting the analysis to 95 children who had vitamin A serum concentrations collected within the 14 days before measles vaccination confirmed all of the findings reported for the 208 children.

Discussion. The effects of vitamin A on the immune system have been the subject of several recent studies in animals and humans. Pasatiempo et al.[9] showed that vitamin A-deficient animals had a significantly diminished antibody response to pneumococcal polysaccharide compared with controls. A clinical trial in Indonesia found that vitamin A-deficient children had a poorer response to vaccination with tetanus toxoid.[10] This study of Jamaican children provides insight into the relationship between serum vitamin A and the immune response to measles vaccination in an unsupplemented population. In this setting vitamin A serum concentrations reflected each child's "steady state" value and not a serum concentration that had been boosted with a one time dose of orally administered vitamin A. This population had a moderate (21%) prevalence of subclinical vitamin A deficiency and yet there was no evidence of adverse or beneficial effects of vitamin A concentration and immune response to measles vaccination.

The high serologic response rate (95%) to measles vaccine identified among the Jamaican children vaccinated at 9 to 12 months in this study is consistent with results from other studies of children in developing countries.[11] The small numbers of nonresponders limited the power of the categoric analysis. However, the more powerful continuous analysis, comparing the actual antibody concentrations with vitamin A serum concentrations demonstrated no significant association between these two variables.

This study also provides additional insight into the relationship among vitamin A, gender and measles vaccine response. Gender differences are of particular interest because of a recent finding by Benn et al.[3] that male recipients of vitamin A supplementation had higher measles antibody concentrations than unsupplemented boys (geometric mean titer ratio, 2.04; 95% CI 1.53 to 2.72), while post vaccination antibody concentrations for supplemented girls were not significantly different from those of unsupplemented girls (geometric mean titer ratio, 1.16; 95% CI 0.85 to 1.58). Because the authors of that trial did not have individual vitamin A serum concentrations available to study, they could only hypothesize that the gender differences might be related to different baseline serum concentrations of vitamin A, with boys having lower serum concentrations and thus being more able to benefit from supplementation. Among Jamaican boys and girls, in the current study individual vitamin A serum concentrations were obtained and permitted the adjustment of the vaccine response by vitamin A value. Analysis of the laboratory data from our study found that the boys and girls had similar vitamin A serum concentrations and measles vaccine responses.

These data suggest that vitamin A serum concentrations do not affect the immune response to measles vaccination when children are vaccinated at 9 months and are not receiving vitamin A supplementation. The benefit from vitamin A supplementation, however, remains one of the most important early childhood interventions in developing countries. Public health programs should continue to make the provision of vitamin A supplementation and measles vaccination a priority.

Acknowledgments. The study was funded by National Cancer Institute Research Contract N01-CP-40548 with the University of the West Indies. We thank Julie Kacergis of Johns Hopkins University for her assistance with the specimen testing; Paulette Palmer, Kevin Brooks and Beverley Cranston of the University of the West Indies for their coordination of patient follow-up and their assistance with the medical record abstractions in Jamaica; Donna Medeiros, formerly of Research Triangle Institute, for her assistance with database management; and Dr. David Vlahov of Johns Hopkins University for his assistance with the early stages of the execution of the study.

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Accepted for publication March 18, 1998.

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Pediatr Infect Dis J 1998 June;17(6):526-528

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